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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,504	06/15/2006	Hua Zhu Ke	PC23170A	7396
28523	7590	06/25/2009	EXAMINER	
PFIZER INC. PATENT DEPARTMENT Bld 114 M/S 114 EASTERN POINT ROAD GROTON, CT 06340			CRUZ, KATHRIEN ANN	
			ART UNIT	PAPER NUMBER
			1617	
			NOTIFICATION DATE	DELIVERY MODE
			06/25/2009	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/596,504	<b>Applicant(s)</b> KE ET AL.	
	<b>Examiner</b> KATHRIEN CRUZ	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 June 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

**Detail Action**

Claims 1-14 are pending.

**Priority**

This application claims benefit of PCT/IB04/04049 (dated 12/06/2004) which claims benefit of provisional application 60/530,939 (dated 12/17/2003).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-6 are rejected under 35 U.S.C.112, first paragraph, because the specification , while being enabling for making and using salts of the claimed compounds, does not reasonable provide enablement for making and using prodrug, solvates or hydrates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. “The factors to be considered [in making an enablement rejection have been summarized as a ) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of tat art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *ex parte formal*, 230 USPQ 546. a) Finding a prodrug,

Art Unit: 1617

solvates or hydrates is an empirical exercise. Predicting if a certain ester of claimed alcohol, for example, is in fact a prodrug, solvates or hydrates, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, solvates or hydrates, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrug, solvates or hydrates is found in the specification on page 21. c) There is no working example of a solvates or hydrates of a compound the formula II. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrugs art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicated the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug,

solvates or hydrates concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence is particularly relevant. f) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved”, and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPQ 1970). g) The breadth of the claims includes all of the hundreds of thousand of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug, solvates or hydrates embraced by claim 1-6.

MPEP 2164.01(a) states, “[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 are rejected under 35 U.S.C. 103 as unpatentable over Cameron et al (U.S. 6,552,067) and Paz (Effect of  $17\beta$ -estradiol or alendronate on the bone desitometry, bone histomorphometry and bone metabolism of ovariectomized rats, Brazillian Journal of Medical Biological Research (2001) 34: 1015-1022).

Cameron teaches that 5-(3-{2S-[3R-Hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid is useful for the treatment of osteoporosis (abstract and example 3M (column 71, lines 25 – column 72, lines 31). Cameron teaches the dosage range of 1-10 mg/kg/day for 30 days in rats (column 26, lines 50).

Cameron does not expressly teach the administration of  $17\beta$ -esterdiol or dosage of  $17\beta$ -esterdiol of approximately 0.01 mg/kg/day.

Paz teaches that  $17\beta$ -estradiol at a dose of 30  $\mu$ g/kg per day for 6 weeks in rats for the treatment of bone loss (e.g. osteoporosis) (see abstract).

It would have been obvious to one of ordinary skills in the art to employ 17 $\beta$ -esterdiol to that 5-(3-{2S-[3R-Hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid for the treatment of osteoporosis (e.g. bone loss). One would have been motivated to employ 17 $\beta$ -esterdiol because 17 $\beta$ -esterdiol is known to be useful in the treatment of bone loss (e.g. osteoporosis) and the combination of 2 compounds known to treat osteoporosis (e.g. bone loss) would enhance the treatment of osteoporosis (e.g. bone loss). As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in *Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.

Therefore, it would have been prima facie obvious to combine that 5-(3-{2S-[3R-Hydroxy-4-(3-trifluoromethyl-phenyl)-butyl]-5-oxo-pyrrolidin-1-yl}-propyl)-thiophene-2-carboxylic acid and 17 $\beta$ -esterdiol composition conjointly in a formulation to treat osteoporosis (e.g. bone loss).

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The

Art Unit: 1617

claims are therefore, properly rejected under 35 U.S.C. 103. In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### **Conclusion**

Claims 1-14 are rejected.

No claims are allowed.

### **Communication**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



Art Unit: 1617

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN CRUZ/  
Examiner, Art Unit 1617

/San-ming Hui/  
Primary Examiner, Art Unit 1617